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EXAMINER	
SALMON, KATHERINE D	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,374	SU, XING	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,22-34 and 36-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,22-34 and 36-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/05/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 1/31/2008. Currently Claims 1-17, 22-34, and 36-44 are pending. Claims 18-21 and 35 have been canceled.

2. The following rejections to Claims 1-17, 22-34, and 36-44 are reiterated, applied as necessitated by amendments, or newly applied. It is noted that the double patenting rejection presented below is newly applied. Response to arguments follows.

3. This action is Non-FINAL.

Withdrawn Rejections

4. The rejection of claims 22-32, 38, and 44 under 35 USC 112/New Matter made in section 6 of the previous office action is moot based on amendments to the claims.
5. The rejection of claims 22-32 under 35 USC 112/second paragraph made in section 7 of the previous office action is moot based on amendments to the claims.

Claim Rejections - 35 USC § 112/New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The following rejection is reiterated from the 35 USC 112/New matter presented in the nonfinal mailed on 10/16/2007.

7. Claims 39-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With regard to Claims 39-40, the claims are drawn to tags attached to the backbone of at least one of the Raman-active oligonucleotide probes or the labeled oligonucleotide probe. Upon review of the specification, the specification does not appear to provide support for attaching labels to the backbone of the probe. The specification does not contemplate attachment to a "backbone". The reply points to Figure 4b as support for a tag on the backbone of the oligonucleotide probe. Figure 4b, however, is merely a representation of probes and tags and does not provide support for the attachment of the tag to a backbone.

These amendments to the claims, therefore, constitute new matter.

Response to Arguments

The reply traverses the rejection. The reply asserts that the independent claim 38 has been amended to remove "backbone" to remove any alleged new matter (p. 11 1st full paragraph). The reply asserts that Figure 4b illustrates AmC6 labels attached to the middle (i.e. the backbone) (GTMN) of the nucleotide probe (p. 11 1st full paragraph).

This argument has been fully considered but has not been found persuasive.

Though there is a figure that illustrates a label attached to a probe it is unclear where the probe would be attached because there is no clear description in the

specification that the label are attached to the backbone. As such in Figure 4b it is not clear the label is actually attached to the backbone.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. The following rejection under 35 USC 112/second paragraph is newly applied as necessitated by amendment.

9. Claims 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39-40 recites the limitation "the backbone" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 38 has been amended to remove the term “the backbone” as such the dependent claims no longer refer to a pending limitation of Claim 38. It is suggested that the claims be amended to correct antecedent basis.

37 CFR 1.132 Declarations

6. The reply of 1/31/2008 has asserted that a 37 CFR 1.132 Declarations by Dr. Xing Su was submitted 9p. 12 2nd paragraph). However, no 37 CFR 1.132 declaration has been submitted for the case.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The following 35 USC 103(a) is necessitated by amendment. It is noted that art used has been presented in the nonfinal office action mailed 10/16/2007. Response to arguments follows.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claim 1-2, 5-7, 9-10, 13-17, 37, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Claim 16) (Abstract). With regard to Claim 1, Cao et al. teaches contacting a target nucleic acid with a plurality of capture probes bound to a substrate forming a single-stranded overhang (p. 1537 1st column top of last paragraph and Figure 1).

Cao et al. teaches contacting the probe-target with a population of Raman-active oligonucleotides which forms a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph and Figure 1). Cao et al. teaches a method in which the probe has a positively charged Raman signal enhancer (Figure 1 and p. 1537 1st column top of last paragraph). Cao et al. teaches the positively charged Raman signal enhancer is a Cy3-labeled alkylthiol capped oligonucleotide (Figure 1 and p. 1537 1st column top of last paragraph).

Faulds et al. teaches that Cy3 is positively charged (p. 668 2nd column 3rd paragraph) and therefore the probe comprises a positively charged enhancer.

With regard to Claim 2, Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (intrinsically generated a detectable signal) (p. 1537 1st column last sentence and 2nd column).

With regard to Claim 5, Cao et al. teaches the use of an AU nanoparticle modified with Cy3-labeled, alkylthiol-capped oligonucleotide strands as probes (p. 1537 1st column top of last paragraph and Figure 1). These probes would be a composite of organic-inorganic nanoparticles.

With regard to Claims 6 and 7, Cao et al. teaches a method of determining the nucleotide position at of a SNP in a bound target sequence (p. 1539 Figure 4).

With regard to Claims 9 and 10, Cao et al. teaches a target of 30 bps and a capture probe and Raman-active oligonucleotide probe with the combined bp of 30, therefore Cao et al. teaches a target which is equal to the combined length of the capture and the Raman-active probe (figure 1).

With regard to Claim 13, the methods of Cao et al. are conducted in the absence of an amplification step.

With regard to Claim 14, Cao et al. teaches a method in which each spot on the microarray is a target: capture probe duplex (abstract). Cao et al. teaches that at least one Raman dye label can be used as a probe, therefore Cao et al. teaches the limitation of 1000 or less molecules of Raman-active probes detected (p. 1537 Figure 1).

With regard to Claim 15, Cao et al. teaches a substrate is a biochip (figure 1).

With regard to Claim 16, Cao et al. teaches SERS (Figure 1 last step of Scheme 1).

With regard to Claim 17, Cao et al. teaches a method of labeling nanoparticles with 6 different dyes and contacting each of the Raman probes to a different probe:target duplex on the array (p. 1538 Figure 2).

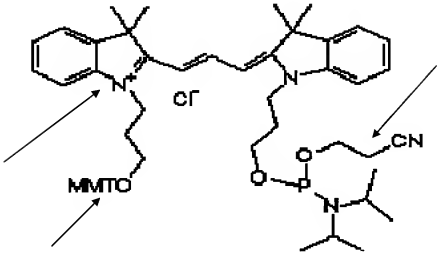
With regard to Claim 37, Cao et al. teaches a single stranded portion that is a constituent of the target nucleic acid (Figure 1).

With regard to Claims 38, Cao et al. teaches a method wherein the label is attached to the 3' nucleotide. The instant specification has not specifically defined the term backbone and therefore it is being interpreted as attachment of the label to any nucleotide of the probe.

Cao et al. teaches the positively charged enhancer but does not indicate the method of making the enhancer so it is not clear from the teachings if the positive charge is present after binding with the probe-target complex.

Mirkin et al. teaches the same method of Cao et al. (it is noted the US Patent application and the Cao et al. reference are the same inventors). With regard to Claim 1, Mirkin et al. teaches the method of attaching the Cy3 linker to the complex (examples 2 p. 10). Mirkin et al teaches the Cy3 modified was purchased from Glen Research (paragraph 158 p. 10).

The following chemical structure is from the Glen Research Catalog.



Mirkin et al. teaches that the oligonucleotide is attached to the phosphoramidite and the linker is attached to the DMT (displayed as MMTO on the figure) (p. 10 paragraph 158) . Therefore the positively charged amine is not effected by the attachment of the linker and the oligonucleotide and would maintain its positive charge after binding to with the probe-target complex.

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to make the Cy3 labeled probe used in the Cao et al. reference using the method of Mirkin et al. with a reasonable expectation of success. It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply a known technique of creating a CY3 labeled probe with the predictable expectation that the Cy3 labeled probe could be used to detect probe hybridization.

Response to Arguments

The reply traverses the rejection. A summary of the arguments made in the reply are summarized below with response to arguments following.

The reply asserts that as discussed in the 37 CFR 1.132 declaration the Cy3 labeled probe taught by Cao et al. cannot maintain a positive charge after binding with the probe-target complex (p. 12 2nd paragraph).

This argument has been fully reviewed but has not been found persuasive.

As discussed, there has been no 37 1.132 declaration submitted by Dr. Xing Su in the instant application. However, Mirkin et al. presents a method of making Cy3 probes which would encompass a Cy3 label that has a positive charge after hybridization. Mirkin et al. teaches that the oligonucleotide is attached to the phosphoramidite and the linker is attached to the DMT (displayed as MMTO on the figure) (p. 10 paragraph 158) . Therefore the positively charged amine is not effected by the attachment of the linker and the oligonucleotide and would maintain its positive charge after binding to with the probe-target complex.

13. Claims 3-4, 8 are rejected under 35 U.S.C. 103(a) as being over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) as applied to Claims 1-2, 5-7, 9-10, 13-17 above and in view of Mirkin et al. (US Patent 6361944 March 26, 2002) (referred to as Mirkin B).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Abstract). Cao et al. teaches contacting a target nucleic acid with a plurality of capture probes bound to a substrate forming a single-stranded overhang (p. 1537 1st column top of last paragraph and Figure 1).

Cao et al. teaches contacting the probe-target with a population of Raman-active oligonucleotides which forms a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph and Figure 1). Cao et al. teaches a method in which the probe has a positively charged Raman signal enhancer (Figure 1 and p. 1537 1st column top of last paragraph). Cao et al. teaches the positively charged Raman signal enhancer is a Cy3-labeled alkylthiol capped oligonucleotide (Figure 1 and p. 1537 1st column top of last paragraph). Faulds et al. teaches that Cy3 is positively charged (p. 668 2nd column 3rd paragraph) and therefore the probe comprises a positively charged enhancer.

However, Cao et al. and Mirkin et al. do not teach Raman-active probes that comprise less than 5 or no purine residues.

Mirkin B teaches a method of detecting a nucleic acid using nanoparticles (Abstract). With regard to Claims 3-4, Mirkin B teaches a probe which comprises no purines (Seq Id No. 9 Figure 10).

With regard to Claim 8, Mirkin B teaches a method to detect multiple nucleotides mismatches in a target (e.g. a series of nucleotide occurrences at adjacent positions (Figure 12F).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. and Mirkin et al. to include the probe with no purines as taught by Mirkin B. The ordinary artisan would have been motivated to modify the method of Cao et al. and Mirkin et al. to include the probe with no purines as taught by Mirkin B because Mirkin B teaches that nanoparticles bearing only pyrimidine oligonucleotide bind in a sequence specific manner at purine and pyrimidine sites (Column 58 lines 15-25). Mirkin B. teaches that the binding allows for formation of triple-stranded complexes such that nanoparticle probes can be used for double stranded targets (Column 58 lines 15-25). Therefore the ordinary artisan would be motivated to use the probes of Mirkin B to detect double stranded targets.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is present below with response to arguments following.

The reply asserts that Mirkin B does not render the limitations of Claim 1 obvious (p. 14 2nd paragraph). This arguments has been fully reviewed but has not been found persuasive. As discussed in the previous 35 USC 103(a) rejection the combination of Cao et al. and Mirkin et al. teaches all claimed limitations of Claim 1. The further

combination of Cao et al., Mirkin et al., and Mirkin B teaches all the limitations of Claims 3-4, 8.

14. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) as applied to Claims 1-2, 5-7, 9-10, 13-17 above and in view of Pastinen et al. (Genome Research July 2000 Vol. 10(7) p. 1031).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Abstract). Cao et al. teaches contacting a target nucleic acid with a plurality of capture probes bound to a substrate forming a single-stranded overhang (p. 1537 1st column top of last paragraph and Figure 1).

Cao et al. teaches contacting the probe-target with a population of Raman-active oligonucleotides which forms a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph and Figure 1). Cao et al. teaches a method in which the probe has a positively charged Raman signal enhancer (Figure 1 and p. 1537 1st column top of last paragraph). Cao et al. teaches the positively charged Raman signal enhancer is a Cy3-labeled alkylthiol

capped oligonucleotide (Figure 1 and p. 1537 1st column top of last paragraph). Faulds et al. teaches that Cy3 is positively charged (p. 668 2nd column 3rd paragraph) and therefore the probe comprises a positively charged enhancer.

However, Cao et al. and Mirkin et al. do not teach detecting the nucleotide sequence of the entire target by aligning detected target sequences.

Pastinen et al. teaches a method of genotyping by allele-specific primer extension on a microarray (abstract).

With regard to Claim 11, Pastinen et al. teaches genotyping in which using primer extension a user can determine the sequence of the extended target (Abstract). Pastinen et al. teaches using a array of a multiplex of primers each specifically near a SNP area of detections (p. 1033 1st column last sentence and second column 1st paragraph). It is obvious in the teaching that a user can make an array composes of probes that when extended can detect nucleotides. After detection of the nucleotide from each primer extension the complete sequence of the target could be determining by aligning the nucleotides from each probe.

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. and Mirkin et al. to include the step of sequencing the target as taught by Pastinen et al. The ordinary artisan would have been motivated to modify the method of Cao et al. and Mirkin et al. to include the step of sequencing the target as taught by Pastinen et al. a method to perform high-throughput genotyping of samples in a parallel analysis method. The

ordinary artisan would be motivated to use the method of Pastinen et al. to sequence the entire target in a quick assay to determine the entire sequence of the target.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is present below with response to arguments following.

The reply asserts that Pastinen et al. does not render the limitations of Claim 1 obvious (p. 4 last paragraph). This arguments has been fully reviewed but has not been found persuasive. As discussed in the previous 35 USC 103(a) rejection the combination of Cao et al. and Mirkin et al. teaches all claimed limitations of Claim 1. The further combination of Cao et al., Mirkin et al., and Pastinen et al. teaches all the limitations of Claims 11.

15. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) as applied to Claims 1-2, 5-7, 9-10, 13-17 above and in view of Lane et al. (US Patent 5,770,365 June 23, 1998).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Abstract). Cao et al. teaches contacting a target nucleic acid with a plurality of capture probes bound to a substrate forming a single-stranded overhang (p. 1537 1st column top of last paragraph and Figure 1).

Cao et al. teaches contacting the probe-target with a population of Raman-active oligonucleotides which forms a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph and Figure 1). Cao et al. teaches a method in which the probe has a positively charged Raman signal enhancer (Figure 1 and p. 1537 1st column top of last paragraph). Cao et al. teaches the positively charged Raman signal enhancer is a Cy3-labeled alkylthiol capped oligonucleotide (Figure 1 and p. 1537 1st column top of last paragraph). Faulds et al. teaches that Cy3 is positively charged (p. 668 2nd column 3rd paragraph) and therefore the probe comprises a positively charged enhancer.

However, Cao et al. and Mirkin et al. do not teach a method in which the capture probe and the oligonucleotide probe are ligated.

Lane et al. teaches a method of using nucleic acid capture moieties to detect nucleic acid sequences (Column 4, lines 19-25). Lane et al. teaches a labeled probe complementary to a target-complementary region of the capture moiety that is immobilized on insoluble support (Column 11, lines 30-35). With regard to Claim 12,

Lane et al. teaches a method in which the detectable probe is ligated to the capture probe (a duplex-binding ligand binding site) (Figure 3).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. and Mirkin et al. to further include the use ligated probes as taught by Lane et al. The ordinary artisan would have been motivated to improve the method of Cao et al. and Mirkin et al. because Lane et al. teaches that the ligation method can be used for the detection of nucleic acid sequences, which do not occur near the terminus of an intact target strand (Column 12, lines 15-20).

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is present below with response to arguments following.

The reply asserts that Lane et al. does not render the limitations of Claim 1 obvious (p. 4 last paragraph). This arguments has been fully reviewed but has not been found persuasive. As discussed in the previous 35 USC 103(a) rejection the combination of Cao et al. and Mirkin et al. teaches all claimed limitations of Claim 1. The further combination of Cao et al., Mirkin et al., and Lane et al. teaches all the limitations of Claims 12.

16. Claims 22-24, 26-27, and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application

Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) as applied to Claims 1-2, 5-7, 9-10, 13-17 above and in view of Chan et al. (US Patent Application Publication March 27, 2003) and Corbierre et al. (Journal of American Chem. Soc 2001 Vol. 123 p. 10411).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Abstract). Cao et al. teaches contacting a target nucleic acid with a plurality of capture probes bound to a substrate forming a single-stranded overhang (p. 1537 1st column top of last paragraph and Figure 1).

With regard to Claim 22, Cao et al. teaches contacting the probe-target with a population of Raman-active oligonucleotides which forms a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph and Figure 1). Cao et al. teaches detecting the fluorescent signal.

With regard to Claim 23, Cao et al. teaches that a florescent signal is detected (Figure 2).

With regard to Claim 26, Cao et al. teaches that a Raman spectra is detected (Figure 2).

With regard to Claim 27, Cao et al. teaches comparing the signal to standard known Raman spectra labels (p. 1538 1st column 2nd paragraph). Therefore Cao et al.

compares the detected spectra with known spectrum to identify the nucleotide occurrence.

However, Cao et al. and Mirkin et al. do not teach a method of labeling the target with two labels, applying premade aggregates of metallic colloids to the probe-target, and applying an alternating current.

Chan et al. teaches a method for spatial resolution of signal detection (Abstract). With regard to Claim 22, Chan et al. teaches a method of passing a target through an optical detector to read florescent signals (p. 12 paragraphs 114 and 115). Chan et al. teaches the probe can be labeled with FRET labels (e.g. two labels on the probe) (paragraph 148 p. 16). Chan et al. teaches that the target nucleotide is pulled through the nanoslit of the channel by applying an alternating current (AC current) filed to the metal layer (p. 14 paragraph 132).

With regard to Claim 24, Chan et al. teaches the probe can be labeled with FRET labels (paragraph 148 p. 16).

With regard to Claim 29, Chan et al. teaches determining a series of nucleotide occurrences for one target by determination of a population of labeled probes (Figure 2 and paragraph 41 p. 4).

With regard to Claim 30, Chan et al. teaches passing the complexes through an optical detector to read the fluorescent signal (p. 12 paragraph 115).

With regard to Claim 31, Chan et al. teaches an interactor station comprised of the channel and the optical detector (e.g. a microelectromechical system) (p. 12 paragraph 115).

With regard to Claim 32, Chan et al. teaches that the target nucleotide is pulled through the nanoslit of the channel by applying an alternating current (AC current) filed to the metal layer (p. 14 paragraph 132). Chan et al. teaches the optical system uses radiation modulated frequencies (AC current oscillations) in the range of 10 MHz to 1 GHz (p. 15 paragraph 138).

With regard to Claim 22, Corbierre et al. teaches a method of synthesizing nanoparticles such as gold before incorporation (p. 10411 2nd paragraph). Corbierre et al. teaches a method of making pre-made nanoparticles (p. 10411 2nd paragraph).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. and Mirkin et al. to further include the use of a AC current and two label FRET system as taught by Chan et al. and premade gold nanoparticles as taught by Corbierre et al. The ordinary artisan would have been motivated to modify the method of Cao et al. and Mirkin et al. to further include the use of a AC current and two label FRET system as taught by Chan et al. because Chan et al. teaches a method of linear analysis of DNA which can allow for the development of specific sequences to be used in sequence-specific tagging and differentially tagging to increase resolution (p. 1 paragraph 3 and 4). The ordinary artisan would have been motivated to modify the method of Cao et al. and Mirkin et al. to further include the use of a premade gold nanoparticles as taught by Corbierre et al., because Corbierre et al. teaches that premade nanoparticles provides full synthetic control over the making of the nanoparticle (p. 10412 last paragraph).

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is present below with response to arguments following.

The reply asserts that Chan et al. and Corbierre et al. do not render the limitations of Claim 1 obvious (p. 4 last paragraph). This arguments has been fully reviewed but has not been found persuasive. As discussed in the previous 35 USC 103(a) rejection the combination of Cao et al. and Mirkin et al. teaches all claimed limitations of Claim 1. The further combination of Cao et al., Mirkin et al., Chan et al. and Corbierre et al. teaches all the limitations of Claims 22-24, 26-27, and 29-32.

The reply asserts that Claim 22 recites that the first label affecting the Raman spectra or florescent signal generated by the second label based on the orientation of the first label to the second label (p. 14 3rd paragraph). The reply asserts that Chan does not teach or suggest a first label affecting the Raman spectral generated by the second label based on a change in the orientation of a label (p. 14 3rd paragraph).

This argument has been thoroughly reviewed but has not been found persuasive.

Chan et al. teaches a method of passing a target through an optical detector to read florescent signals (p. 12 paragraphs 114 and 115). Chan et al. teaches the probe can be labeled with FRET labels (e.g. two labels on the probe) (paragraph 148 p. 16). Chan et al. teaches that the target nucleotide is pulled through the nanoslit of the channel by applying an alternating current (AC current) filed to the metal layer (p. 14 paragraph 132). Therefore Chan et al. teaches that depending on the label on the first nucleotide the target is pulled through the nanoslit.

17. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Chan et al. (US Patent Application Publication March 27, 2003) as applied to claims 22-24, 26-27, and 29-32 above and further in view of Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002).

Neither Cao et al., Mirkin et al. or Chan et al. teach FRET labels of TAMRA and ROX.

With regard to Claim 25, Bruchez, Jr. et al. teaches that the flurophores, which can be used as labels, include TAMRA and ROX (p. 13 paragraph 151).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. Mirkin et al. and Chan et al. to further include any type of FRET labels including TAMRA and ROX as presented by Bruchez Jr. et al. The use of FRET labels is well known in the art and the use of different types of FRET labels are interchangeable. Therefore the ordinary artisan would use any type of FRET label for the method of Cao et al. Mirkin et al. and Chan et al. including TAMRA and ROX to detect nucleotide occurrences on a target strand.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is present below with response to arguments following.

The reply asserts that Bruchez Jr. et al. do not render the limitations of Claim 22 obvious (p. 4 last paragraph). This arguments has been fully reviewed but has not been found persuasive. As discussed in the previous 35 USC 103(a) rejection the combination of Cao et al. Mirkin et al. and Chan et al. teaches all claimed limitations of Claim 22. The further combination of Cao et al., Mirkin et al., Chan et al. and Bruchez Jr. et al. teaches all the limitations of Claims 25.

18. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Chan et al. (US Patent Application Publication March 27, 2003) as applied to claims 22-24, 26-27, and 29-32 above and further in view of Livak et al. (US Patent 5,723,591 March 3, 1998).

Neither Cao et al. Mirkin et al or Chan et al. teaches the two labels located about 3-6 nm apart.

With regard to Claim 28, Livak et al. teaches that the quencher molecule and reporter should be between 6-16 nucleotides (Column 3, line 63). The distance between nucleotides is 0.23 nm, therefore the distance between a reporter and quencher can be between 1.38 to 3.68 nm apart (between 3-6 nm).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. Mirkin et al. and Chan et al. to further include distance limitation as taught by Livak et al. The ordinary artisan would have been motivated to modify the method of Cao et al. Mirkin et al. and Chan et al. to further include distance limitation as taught by Livak et al. because Livak et al. teaches that there is a distance that must be maintained between the quencher and reporter in order for the quencher to be able to quench the reporter in the assay (Column 3, lines 60-65).

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is present below with response to arguments following.

The reply asserts that Livak et al. do not render the limitations of Claim 28 obvious (p. 4 last paragraph). This arguments has been fully reviewed but has not been found persuasive. As discussed in the previous 35 USC 103(a) rejection the combination of Cao et al. Mirkin et al. and Chan et al. teaches all claimed limitations of Claim 22. The further combination of Cao et al., Mirkin et al., Chan et al. and Livak et al. teaches all the limitations of Claims 28.

19. Claims 33, 39, and 43 are rejected under 35 U.S.C. 103(a) as being over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913

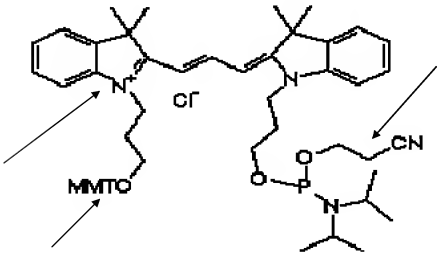
www.glenresearch.com) in view of Garimella et al. (US Patent Application Publication 2003/0082588 May 1, 2003).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Abstract). With regard to Claim 33, Cao et al. teaches irradiating the nucleic acid with light (figure 1) and detecting a Raman signal generated (Figure 2).

With regard to Claim 39, Cao et al. teaches contacting a target nucleic acid with a plurality of capture probes bound to a substrate forming a single-stranded overhang (p. 1537 1st column top of last paragraph and Figure 1).

Mirkin et al. teaches the same method of Cao et al. (it is noted the US Patent application and the Cao et al. reference are the same inventors). With regard to Claim 1, Mirkin et al. teaches the method of attaching the Cy3 linker to the complex (examples 2 p. 10). Mirkin et al teaches the Cy3 modified was purchased from Glen Research (paragraph 158 p. 10).

The following chemical structure is from the Glen Research Catalog.



Mirkin et al. teaches that the oligonucleotide is attached to the phosphoramidite and the linker is attached to the DMT (displayed as MMTO on the figure) (p. 10 paragraph 158) . Therefore the positively charged amine is not effected by the attachment of the linker and the oligonucleotide and would maintain its positive charge after binding to with the probe-target complex.

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to make the Cy3 labeled probe used in the Cao et al. reference using the method of Mirkin et al. with a reasonable expectation of success. It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply a known technique of creating a CY3 labeled probe with the predictable expectation that the Cy3 labeled probe could be used to detect probe hybridization.

However, Cao et al. does not teach a positively charged Raman signal enhancer which comprises a primary amine Raman signal enhancer having an alkyl chain of 1 to 25 carbon atoms.

With regard to Claim 33 and 43, Garimella et al. teaches an amino functionalized gold nanoparticle attached to a probe (paragraph 65 p. 5). Garimella et al. teaches that there is a linker chain of 20 amines (paragraph 65 p. 5).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. to include a positively charged Raman signal enhancer which comprises a primary amine Raman signal enhancer having an alkyl chain of 1 to 25 carbon atoms as taught by Garimella et

al. The ordinary artisan would have been motivated to modify the method of Cao et al. to include a positively charged Raman signal enhancer which comprises a primary amine Raman signal enhancer having an alkyl chain of 1 to 25 carbon atoms as taught by Garimella et al. because Garimella et al. teaches that the linker facilitates hybridization with a target by increasing the separation between the oligonucleotide probe and the nanoparticle (p. 5 paragraph 57).

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is present below with response to arguments following.

The reply asserts that Garimella et al. do not render the limitations of Claim 33 obvious (p. 4 last paragraph). This arguments has been fully reviewed but has not been found persuasive. As discussed in the previous 35 USC 103(a) rejection the combination of Cao et al. Mirkin et al. and Garimella et al. teaches all claimed limitations of Claim 23.

20. Claims 34, 36, and 40 are rejected under 35 U.S.C. 103(a) as being over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Garimella et al. (US Patent Application Publication 2003/0082588 May 1, 2003) as applied to Claims 33, 39, and 43 and further in view of Mirkin et al. (US Patent 6361944 March 26, 2002) (referred to as Mirkin B).

With regard to Claims 40, Cao et al. teaches a method wherein the label is attached to the 3' nucleotide. The instant specification has not specifically defined the term backbone and therefore it is being interpreted as attachment of the label to any nucleotide of the probe.

Neither Cao et al Mirkin et al. or Garimella et al. teach a nucleic acid consisting of only pyrimidine residues or attaching the Raman tag to the backbone of the nucleic acid.

Mirkin B teaches a method of detecting a nucleic acid using nanoparticles (Abstract). With regard to Claims 34 and 36, Mirkin B teaches a probe which comprises no purines (Seq Id No. 9 Figure 10).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al Mirkin et al. and Garimella et al. to include the probe with no purines as taught by Mirkin B The ordinary artisan would have been motivated to modify the method of Cao et al Mirkin et al. and Garimella et al. to include the probe with no purines as taught by Mirkin B because Mirkin B teaches that nanoparticles bearing only pyrimidine oligonucleotide bind in a sequence specific manner at purine and pyrimidine sites (Column 58 lines 15-25). Mirkin B teaches that the binding allows for formation of triple-stranded complexes such that nanoparticle probes can be used for double stranded targets (Column 58 lines 15-25). Therefore the ordinary artisan would be motivated to use the probes of Mirkin B to detect double stranded targets.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is present below with response to arguments following.

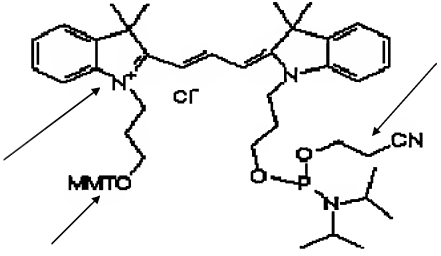
The reply asserts that Mirkin B do not render the limitations of Claim 34 obvious (p. 4 last paragraph). This arguments has been fully reviewed but has not been found persuasive. As discussed in the previous 35 USC 103(a) rejection the combination of Cao et al Mirkin et al. and Garimella et al. teaches all claimed limitations of Claim 33. The further combination of Cao et al Mirkin et al. and Garimella et al. and Mirkin B teaches all the limitations of Claims 34.

21. Claims 41-42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) in view of Garimella et al. (US Patent Application Publication 2003/0082588 May 1, 2003)in view of Corbierre et al. (Journal of American Chem. Soc 2001 Vol. 123 p. 10411).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Abstract). Cao et al. teaches contacting a target nucleic acid with a plurality of capture probes bound to a substrate forming a single-stranded overhang (p. 1537 1st column top of last paragraph and Figure 1).

Mirkin et al. teaches the same method of Cao et al. (it is noted the US Patent application and the Cao et al. reference are the same inventors). With regard to Claim 1, Mirkin et al. teaches the method of attaching the Cy3 linker to the complex (examples 2 p. 10). Mirkin et al teaches the Cy3 modified was purchased from Glen Research (paragraph 158 p. 10).

The following chemical structure is from the Glen Research Catalog.



Mirkin et al. teaches that the oligonucleotide is attached to the phosphoramidite and the linker is attached to the DMT (displayed as MMTO on the figure) (p. 10 paragraph 158) . Therefore the positively charged amine is not effected by the attachment of the linker and the oligonucleotide and would maintain its positive charge after binding to with the probe-target complex.

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to make the Cy3 labeled probe used in the Cao et al. reference using the method of Mirkin et al. with a reasonable expectation of success. It would have been

obvious to one of ordinary skill in the art at the time the invention was made to apply a known technique of creating a CY3 labeled probe with the predictable expectation that the Cy3 labeled probe could be used to detect probe hybridization.

Cao et al. however does not teach premade aggregates of nanoparticles.

With regard to Claim 41-42, Corbierre et al. teaches a method of synthesizing nanoparticles such as gold before incorporation (p. 10411 2nd paragraph). Corbierre et al. teaches a method of making pre-made nanoparticles (p. 10411 2nd paragraph).

With regard to Claim 44, Corbierre et al. teaches making the nanoparticles in lithium triethylborohydride (monovalent salt) (p. 10411 2nd column 2nd paragraph).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. to further include premade gold nanoparticles as taught by Corbierre et al. The ordinary artisan would have been motivated to modify the method of Cao et al. to further include the use of a premade gold nanoparticles as taught by Corbierre et al., because Corbierre et al. teaches that premade nanoparticles provides full synthetic control over the making of the nanoparticle (p. 10412 last paragraph).

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is present below with response to arguments following.

The reply asserts that Corbierre et al. do not render the limitations of Claim 41 obvious (p. 4 last paragraph). This arguments has been fully reviewed but has not been found persuasive. As discussed in the previous 35 USC 103(a) rejection the

combination of Cao et al. Mirkin et al. teaches all claimed limitations of a positively charged label.

22. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Faulds et al. (Talanta 2005 vol. 67 p. 667) in view of Mirkin et al. (US Patent Application Publication 2003/0211488 November 13, 2003) as evidenced by Glen Research Catalog (Catalog Number 105913 www.glenresearch.com) as applied to Claims 1-2, 5-7, 9-10, 13-17, 37, 38 and further in view of Vo-Dinh (US Patent 5721102 2/24/1998).

Cao et al. and Mirkin et al. teaches a method of determining a nucleotide sequence of a target nucleic acid using a positively charged Raman signal enhancer, however, Cao et al. and Mirkin et al. do not teach a method wherein the heteroatom excludes N, O, and S.

With regard to Claim 45, Vo-Dinh et al. teaches a method of labeling probes with Raman labels (Column 6 lines 47-55). Vo-Dinh et al. teaches that the Raman label can include structures such as phosphorus (column 7 lines 8).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method of Cao et al. and Mirkin et al. to use phosphorus labels as taught by Vo-Dinh et al. The ordinary artisan would be motivated to modify the method of Cao et al. and Mirkin et al. to use phosphorus labels as taught by Vo-Dinh et al. because Vo-Dinh et al. teaches that phosphorus are inert to hybridization (column 12 lines 8-11). Therefore the ordinary artisan would be motivated to use a

label which would not interact during the hybridization step in order to reduce background noise.

Double Patenting

23. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

24. Claims 1, 4, and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-3 of copending Application No. 11414681. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1, 4, and 43 of the pending application are drawn to a method comprising a light source, a nucleic acid comprising a positively charged enhancer which is an amine, and detection of the Raman signal, which are identical in steps to Claims 1-3 of application 11/414681.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claims 1, 4, and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-4 of copending Application No. 11414611. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1, 4, and 43 of the pending application are drawn to a method comprising a light source, a nucleic acid comprising a positively charged enhancer which is an amine, and detection of the Raman signal, which are identical in steps to Claims 1-4 of application 11/414611.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

26. No Claims are allowed.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Examiner, Art Unit 1634

/Carla Myers/
Primary Examiner, Art Unit 1634